REMARKS

Upon entry of this amendment, claims 4-6, 8-9, 15 and 17-18 are pending in the instant application. Claims 4-6, 8, 15 and 17-18 have been amended, and claims 7 and 16 have been cancelled herein without prejudice or disclaimer. Applicant reserves the right to prosecute that subject matter, as well as the originally presented claims, in continuing applications.

Unless otherwise noted, all page and line numbers used herein refer to the page and line numbers used in the clean version of the Second Substitute Specification presented herewith. Support for the claim amendments presented herein is found throughout the specification and in the claims as originally filed. For example, support for the polypeptides consisting of the amino acid sequence of PyroGlu-LKCYTCKEPMTSAAC (SEQ ID NO: 1), as recited by amended claims 4-7, is found at least at page 1, lines 19-21; at page 2, lines 5-14 and at page 2, lines 18-28 of the Second Substitute Specification. Support for the SDS-activated polypeptide recited by amended claim 17 is found at least at page 2, lines 26-28; at page 3, lines 12-14; and at page 4, lines 6-17 of the Second Substitute Specification. Support for the methods of killing a tumor cell, as recited by amended claims 8 and 18, is found at least at page 1, lines 19-21; at page 2, lines 18-28; and in Example 1 at page 3, line 4 through page 4, line 17 of the Second Substitute Specification. Support for the methods of activating an anti-tumor polypeptide, as recited by amended claim 15, is found in the specification at least at page 2, lines 26-28; at page 3, lines 12-14; and at page 4, lines 6-17 of the Second Substitute Specification.

Accordingly, no new matter has been added by this amendment.

1. Objections Under 35 U.S.C. §132 and Substitute Specification

Applicants submitted a Substitute Specification in conjunction with the previous Amendment and Response, filed on September 4, 2003. The Examiner has objected to the September 4, 2003 Substitute Specification (hereinafter "First Substitute Specification") under 35 U.S.C. §132 as introducing new matter into the specification. The Examiner has indicated that the First Substitute Specification was not entered, because this specification requested that "the N-terminal amino acid be changed from pyroglutamic acid to glutamic acid." (Office Action, page 2).

Applicant submits herewith a Second Substitute Specification under the provisions of 37 CFR § 1.125(b) and (c). This Second Substitute Specification discloses an ANUP peptide wherein the N-terminal amino acid of SEQ ID NO:1 is pyroglutamic acid, as recited by the originally filed specification. Also, Applicant has amended the specification in accordance with the preferred arrangement of the specification. In particular, Applicant has re-arranged certain sections of the as-filed specification, but Applicant has not added any additional information. Accordingly, no new matter has been added to the Second Substitute Specification presented herewith. Applicant, therefore, requests that the Examiner withdraw this objection and replace the as-filed specification with the Second Substitute Specification submitted herewith.

2. Claim Rejections Under 35 U.S.C. § 112, First Paragraph (Written Description)

Claims 4-9 and 15-18:

The Examiner has rejected claims 4-9 and 15-18 under 35 U.S.C. §112, first paragraph for lack of written description. According to the Examiner, "it does not appear that support exists for a peptide that comprises SEQ ID NO: 1". (Office Action, p. 3).

As suggested by the Examiner, Applicants have amended the pending claims to recite polypeptides that consist of the following amino acid sequence PyroGlu-LKCYTCKEPMTSAAC (SEQ ID NO: 1), and methods of using or activating such polypeptides. The 16 amino acid-long polypeptide of SEQ ID NO:1 is described throughout the specification. For example, the amino acid sequence of this polypeptide is disclosed page 2, lines 5-14.

The anti-tumor effects of this peptide, namely the induction of apoptosis, and methods of using this peptide to induce apoptosis of a tumor cell, are described throughout the specification and demonstrated in Example 1. As described at page 1, lines 19-21, the 16 amino acid-long peptide of the invention ("P_{16}") has been shown to exert its anti-tumor action on human breast cancer tumor cells by inducing apoptosis, as electron microscopy studies indicated complete degradation of the cancer cells contacted with the P_{16} peptide.

Methods of using the anti-tumor P_{16} peptide to kill a tumor cell by inducing apoptosis are disclosed in Example 1. In this Example, human breast tumor cells contacted with the P_{16} peptide were subsequently exposed to a red marker dye and lysed. As described, *e.g.*, at page 3,

lines 23-26, the level of dye from the lysed cells acts as an indicator of the anti-tumor effect of the P_{16} peptide. As shown on page 4, lines 1-5, the P_{16} peptide demonstrated anti-tumor cell activity on the human breast tumor cells. Thus, the specification fully describes the claimed anti-tumor peptides and methods of using these peptides to induce apoptosis of a tumor cell.

A method of activating the P_{16} peptide using SDS, as well as an SDS-activated P_{16} peptide, are also described throughout the specification. For example, the passage at page 4, lines 10-17, demonstrates that, in the presence of SDS, the P_{16} peptide possesses anti-tumor activity, and moreover, the anti-tumor activity of the peptide increases as the concentration of SDS present increases. The anti-tumor effects of such SDS-activated peptides is described, *e.g.*, in Example 1 at page 3, lines 9-27, which demonstrates that P_{16} peptide diluted in SDS kills tumor cells. Thus, SDS-activated peptides, anti-tumor SDS-activated peptides, methods of activating the P_{16} peptide using SDS and methods of using SDS-activated peptides to kill tumor cells are described by the specification.

In light of the teachings in the specification and the claim amendments presented herein, Applicant respectfully submits that the polypeptides and methods of the amended claims are fully supported by the instant specification in such a manner as to allow a person skilled in the art to conclude that Applicant had possession of the claimed invention. Accordingly, Applicants requests the withdrawal of this rejection.

Claims 4 and 17:

The Examiner has also indicated that the phrase "a composition comprising" in reference to SEQ ID NO:1 also lacks sufficient written description. According to the Examiner, the specification lacks descriptive support for any and all compositions that contain the peptide of SEQ ID NO:1, as "one or two examples of a species does not amount to a description of a genus." (Office Action, pages 5-6).

Claims 4 and 17 have been amended herein to recite polypeptides of the claimed invention, rather than compositions. In particular, claim 4 has been amended to recite a purified synthetic polypeptide consisting of the amino acid sequence of SEQ ID NO:1, while amended claim 17 is directed to an SDS-activated anti-tumor polypeptide that consists of the amino acid sequence of SEQ ID NO:1. As described above, these claimed P_{16} polypeptides are described

throughout the specification (*see e.g.*, page 1, lines 19-21; page 2, lines 5-14; page 2, lines 18-28; page 3, lines 12-14; and page 4, lines 1-17 of the Second Substitute Specification). Thus, the amended claims are fully supported by the instant disclosure, and this rejection should be withdrawn.

Claim 6:

The Examiner has also rejected claim 6 for lack of sufficient written description. According to the Examiner, this claim is directed to peptide activation by contact with any and all detergents, but there is no descriptive support for any detergent other than SDS.

Applicants note that claim 6 has been amended to recite an anti-tumor polypeptide consisting of the amino acid sequence of SEQ ID NO:1, wherein said polypeptide induces apoptosis in a tumor cell, and wherein the anti-tumor polypeptide is activated by contact with sodium dodecyl sulfate (SDS). Thus, the amended claim is not directed to "any and all detergents". Rather, this claim is directed to activation by contacting a polypeptide of the claimed invention with a specific detergent, SDS. As described above, SDS-activated P_{16} peptides are disclosed throughout the specification (*see e.g.*, page 2, lines 26-28; page 3, lines 12-14; and page 4, lines 6-17 of the Second Substitute Specification). Accordingly, Applicant requests that the Examiner withdraw this rejection.

SEQ ID NO:1:

The Examiner has also rejected the recitation of SEQ ID NO:1 in the claims as new matter "because of the presence of the pyroGlu residue at the N-terminus."

In the Second Substitute Specification submitted herewith, the polypeptide of the claimed invention is presented on page 2, lines 5-14: PyroGlu-LKCYTCKEPMTSAAC and given the sequence identifier SEQ ID NO:1. All references to SEQ ID NO:1 used herein refer to the sequence presented at page 2, lines 5-14 of the Second Substitute Specification. In addition, all references to SEQ ID NO:1 in the amended claims are accompanied by the sequence shown on page 2, lines 5-14 of the Second Substitute Specification. Therefore, this rejection should be withdrawn.

In addition, Applicant submits herewith paper and electronic copies of a Substitute Sequence Listing for the nucleotide sequences and amino acid sequences disclosed in the

specification in compliance with the requirements for patent applications containing nucleotide sequences and/or amino acid sequence disclosures under 37 C.F.R. §§ 1.821-1.825. This Substitute Sequence Listing presents the amino acid sequence of SEQ ID NO:1 as PyroGlu-LKCYTCKEPMTSAAC. Applicants request that the Examiner replace the Sequence Listing filed on September 4, 2003 with the Substitute Sequence Listing submitted herewith.

3. Claim Rejections Under 35 U.S.C. § 112, First Paragraph (Enablement)

Claims 8, 9 and 18 have been rejected under 35 U.S.C. §112, first paragraph for lack of enablement. According to the Examiner, these claims encompass both *in vitro* and *in vivo* methods of killing a tumor cell, and "enablement is lacking, at least for the case of achieving the 'contacting' by administering the peptide to a tumor-bearing mammal." (Office Action, p. 8).

Claims 8-9 have been amended herein to recite methods of killing a tumor cell by contacting the tumor cell with a polypeptide consisting of the amino acid of SEQ ID NO:1 for a time and under conditions effective to kill the tumor cell by apoptosis. Such methods are described at least at page 1, lines 19-21; at page 2, lines 18-28; and in Example 1 at page 3, line 4 through page 4, line 17 of the Second Substitute Specification in such a way as to allow one of ordinary skill in the art to make and/or use these claimed methods.

The data provided in the specification are representative of standard *in vitro* cell-based assays, which are used by those skilled in the art to evaluate performance of a composition *in vivo*. Results of such *in vitro* assays are generally regarded as predictive of performance *in vivo*.

ANUP polypeptides have also been tested *in vivo* using a well-known animal model for clinical cancer, which was described in the first Declaration Under 37 C.F.R. §1.132 of Paul DiTullio ("DiTullio Declaration I"), filed on September 4, 2003. Applicant submits herewith a second Declaration Under 37 C.F.R. §1.132 of Paul DiTullio ("DiTullio Declaration II"). As described in the DiTullio Declaration II, the ANUP polypeptides tested included an N-terminal ANUP peptide having a pyroglutamic acid residue at the N-terminus, an N-terminal ANUP peptide having a glutamic acid residue at the N-terminus, and the full-length ANUP protein (purified from plasma). This Declaration confirms that both of the N-terminal ANUP peptides demonstrated anti-tumor activity by killing tumor cells in the art-recognized tumor model.

Thus, the data obtained using the art-recognized animal model confirms that the *in vitro* data disclosed in the as-filed specification is predictive of anti-tumor activity of the peptides in a tumor-bearing animal. As evidenced by the data presented in the DiTullio Declarations, the claimed compositions and methods predictably lead to tumor cell killing. Accordingly, the as-filed specification is enabling for the scope of the amended claims, and this rejection should be withdrawn.

4. Claim Rejections Under 35 U.S.C. § 112, second paragraph

Claims 5 and 15-17 have been rejected under 35 U.S.C. § 112, second paragraph as being indefinite. Claim 16 has been cancelled. The remaining claims are addressed below.

Claim 5:

The Examiner has requested an explanation of the "polypeptide that comprises a specific concentration of polypeptide" recited by claim 5. (Office Action, p. 9).

Applicant notes that claim 5 has been amended herein to recite anti-tumor polypeptides consisting of the amino acid sequence of SEQ ID NO:1. Thus, all references to a "concentration" of an anti-tumor polypeptide have been removed from this claim. Accordingly, this rejection should be withdrawn.

Claim 15:

The Examiner has indicated a grammatical error in claim 15. As suggested by the Examiner, all references to promoting apoptosis "in" a tumor cell have been replaced with the phrase promoting apoptosis "of" of a tumor cell. Applicants requests, therefore, that the Examiner withdraw this rejection.

Claims 16-17:

The Examiner has rejected the phrase "composition" in claims 16 and 17. According to the Examiner, the term "composition" mandates the presence of a second component, but the claims do not recite a second component.

Claim 16 has been cancelled, thereby rendering any rejections of this claim moot. In addition, claim 17 has been amended to recite "an SDS-activated polypeptide", rather than a

composition. Accordingly, amended claim 17 does not require a second component, and this rejection should be withdrawn.

CONCLUSION

On the basis of the foregoing amendments, Applicant respectfully submits that the pending claims are in condition for allowance. If there are any questions regarding these amendments and remarks, the Examiner is encouraged to contact the undersigned at the telephone number provided below.

Respectfully submitted,

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